EXHIBIT 23

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

FODOR et al.

Appln. No. 09/362,089 Group Art Unit: 1643

Filed: July 28, 1999 Examiner: Not known

FOR: A METHOD OF DETECTING NUCLEIC ACIDS

* * *

January 6, 2000

SECOND PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Please enter the following amendments before substantive examination of the present application.

IN THE CLAIMS:

Kindly add the following new claims.

--39. A method of analyzing a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system, whereby one or more of the substrates bind to the target via the reagent;

(b) separating the substrates that bind the target from the substrates that do not bind the target; and

(c) identifying the reagent on a separated substrate using the encoding system.

40. The method of claim 39, wherein the reagent is a probe.

41. The method of claim 40, wherein the probe is an oligonucleotide.

42. The method of claim 39, wherein the target molecule is a polymer.

43. The method of claim 42, wherein the target molecule is a polynucleotide.

44. The method of claim 42, wherein the target molecule is a polypeptide.

45. The method of claim 39, wherein the target molecule is a nucleic acid.

46. The method of claim 39, wherein the substrates are impregnated with a fluorescent molecule.

47. The method of claim 39, wherein the encoding system is a magnetic system, shape encoding system, color encoding system, or a combination thereof.

48. The method of claim 39, wherein the substrates are beads.

49. The method of claim 39, wherein the substrates are fibers.

50. The method of claim 39, wherein the substrates comprise glass.

51. The method of claim 50, wherein the glass is a microscope slide.

52. The method of claim 39, wherein the substrates have a three dimensional contour.

53. The method of claim 39, wherein the reagent is an oligomer.

54. The method of claim 53, wherein the oligomer is a nucleic acid.

55. The method of claim 53, wherein the oligomer comprises nucleotides.

56. The method of claim 53, wherein the oligomer is a peptide.

57. The method of claim 39, wherein the reagent is an oligonucleotide.--

REMARKS

Claims 26-57 are pending.

The amendments to the claims find support throughout the original disclosure. A chart is attached which provides the portions of the specification of U.S. Pat. No. 5,800,992 that disclose the claimed invention. The new claims are directed to an invention disclosed in the specification, but not originally claimed. It is submitted that no new matter has been added by these amendments.

An early and favorable examination on the merits is earnestly requested.

Respectfully submitted,

Cushman Darby & Cushman
Intellectual Property Group of
PILLSBURY MADISON & SUTRO, L.L.P.

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Claims	5,800,992 Specification Support (Col: Line)
1. A method of analyzing a target molecule in a sample, comprising: (a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system, whereby one or more of the substrates bind to the target via the reagent; (b) separating the substrates that bind the target from the substrates that do not bind the target; and (c) identifying the reagent on a separated substrate using the encoding system.	
1. A method of analyzing a target molecule in a sample, comprising:	...the present invention is also applicable to ... general screening of specific interactions. 2:39-41 ...the present invention also provides means for determing specificity of interaction with particular sequences. 11:18-20 The methods make use of a plurality of sequence specific recognition reagents which can also be used for classification of biological samples... (abstract)
(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system, whereby one or more of the substrates bind to the target via the reagent;	Then, the target may be bound to the whole collection of beads and those beads that have appropriate specific reagents on them will bind to the substrate. 21:48-50 As indicated, the sequence specific recognition reagents will often be oligonucleotides which hybridize with fidelity and discrimination to the target sequence. 7:33-35 The hybridization conditions between probe and target should be selected such that the specific recognition interaction, i.e. hybridization, of the two molecules is both sufficiently specific and sufficiently stable. 23:34-37
(b) separating the substrates that bind the target from the substrates that do not bind the target; and	Then a sorting system may be utilized to sort those beads that actually bind the target from those that do not. 21:50-52
(c) identifying the reagent on a separated substrate using the encoding system.	After the relatively small number of beads which have bound the target have been collected, the encoding scheme may be read off to determine the specificity of the reagent on the bead. 21:54-57
2. The method of claim 1, wherein the reagent is a probe.	The specific sequence recognition reagents will typically be oligonucleotide probes... 6:50-51
3. The method of claim 2, wherein the probe is an oligonucleotide.	The specific sequence recognition reagents will typically be oligonucleotide probes... 6:50-51

Claims	5,800,992 Specification Support (Col: Line)
4. The method of claim 1, wherein the target molecule is a polymer.	The production of a substrate having a matrix of positionally defined regions with attached reagents exhibiting known recognition specificity can be used for the sequence analysis of a polymer. 2:35-38 Consequently, the method results in the ability to practically test large numbers of, for example, di, tri, tetra, penta, hexa, hepta, octa, nona, deca, even dodecanucleotides, or larger polynucleotides (or correspondingly, polypeptides). 68:28-31 ...substrates will be applied to evaluating other polymers, e.g., carbohydrates, polypeptides, hydrocarbon synthetic polymers, and the like. 2:42-44
5. The method of claim 4, wherein the target molecule is a polynucleotide.	The present invention also provides methods for analyzing a sequence of a polynucleotide or a polypeptide... 3:14-15
6. The method of claim 4, wherein the target molecule is a polypeptide.	The present invention also provides methods for analyzing a sequence of a polynucleotide or a polypeptide... 3:14-15
7. The method of claim 1, wherein the target molecule is a nucleic acid.	In one refinement, the sequence specific probes are oligonucleotides, applicable to where the target sequences are nucleic acid sequences. 4:28-30 In a nucleic acid hybridization embodiment... 49:66
8. The method of claim 1, wherein the substrates are impregnated with a fluorescent molecule.	Signal detection capability was demonstrated using a low-level standard fluorescent bead kit manufactured by Flow Cytometry Standards and having model no. 824. This kit includes 5.8 μm diameter beads, each impregnated with a known number of fluorescein molecules. 71:23-27
9. The method of claim 1, wherein the encoding system is a magnetic system, shape encoding system, color encoding system, or a combination thereof.	An encoding system may include a magnetic system, a shape encoding system, a color encoding system, or any other encoding system. 21:57-60.
10. The method of claim 1, wherein the substrates are beads.	In one embodiment, the substrates are beads. 3:58 In a bead embodiment... 3:67, 4:1 ...each probe might be attached to a single bead...21:43 Then, the target may be bound to the whole collection of beads... 21:49 In particular, at least four different substrate preparation procedures are available for treating a substrate surface. They are ... and synthetic beads or fibers. 45:63-66 The fourth method utilizes synthetic beads or fibers. 46:42 Signal detection capability was demonstrated using a low-level standard fluorescent bead kit... 71:23-24

Claims	5,800,992 Specification Support (Col: Line)
11. The method of claim 1, wherein the substrates are fibers.	In particular, at least four different substrate preparation procedures are available for treating a substrate surface. They are ... and synthetic beads or fibers. 45:63-66 The fourth method utilizes synthetic beads or fibers. 46:42
12. The method of claim 1, wherein the substrates comprise glass.	Before attachment of reactive groups it is preferred to clean the substrate which is, in a preferred embodiment, a glass substrate such as a microscope slide or cover slip. A roughened surface will be useable but a plastic or other solid substrate is also appropriate. 65:58-62
13. The method of claim 12, wherein the glass is a microscope slide.	Before attachment of reactive groups it is preferred to clean the substrate which is, in a preferred embodiment, a glass substrate such as a microscope slide or cover slip. A roughened surface will be useable but a plastic or other solid substrate is also appropriate. 65:58-62
14. The method of claim 1, wherein the substrates have a three dimensional contour.	...would give additional contour by the 3-dimensional growth of oligomers. 46:49-50
15. The method of claim 1, wherein the reagent is an oligomer.	It will be appreciated by those of skill in the art that the above method could readily be used to simultaneously produce thousands or millions of oligomers on a substrate... 68:24-27
16. The method of claim 15, wherein the oligomer is a nucleic acid.	Protecting groups of the present invention are used in conjunction with solid phase oligomer syntheses, such as peptide syntheses using natural or unnatural amino acids, nucleotide syntheses using deoxyribonucleic and ribonucleic acids, oligosaccharide syntheses, and the like. 37:5-9
17. The method of claim 15, wherein the oligomer comprises nucleotides.	By use of stretches of the degeneracy reducing analogues with other probes in particular combinations, the number of probes necessary to fully saturate the possible oligomer probes is decreased. For example, with a stretch of 12-mers having the central 4-mer of degenerate nucleotides... 17:41-46 Present technology certainly allows production of ten nucleotide oligomers on a solid phase... 19:37-39
18. The method of claim 15, wherein the oligomer is a peptide.	Protecting groups of the present invention are used in conjunction with solid phase oligomer syntheses, such as peptide syntheses using natural or unnatural amino acids, nucleotide syntheses using deoxyribonucleic and ribonucleic acids, oligosaccharide syntheses, and the like. 37:5-9
19. The method of claim 1, wherein the reagent is an oligonucleotide.	In one refinement, the sequence specific probes are oligonucleotides, applicable to where the target sequences are nucleic acid sequences. 4:28-30 In other embodiments, the specific reagent is an oligonucleotide... 3:3-4

EXHIBIT 24

100414

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/362,089	07/28/99	FODOR S	PM-254814

DUE ON
NOV 28 2000

HM12/0828

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EXAMINER	
ZITOMER, S	
ART UNIT	**PAPER NUMBER**
1655	9

DATE MAILED: 08/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

DOCKETED
SEP 11 2000
BY

PILLSBURY MADISON & SUTRO
RECEIVED
AUG 29 2000
WASHINGTON, D.C.

PTO-90C (Rev. 2/95)

2 - Mail Copy

Office Action Summary

Application No.	Applicant(s)
09/362,089	FODOR et al.
Examiner	Group Art Unit
Stephanie Zitomer	1655

RECEIVED NOV 28 2000

☒ Responsive to communication(s) filed on *Jun 13, 1900*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *26-76* is/are pending in the application.

Of the above, claim(s) *26-38* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *39-76* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

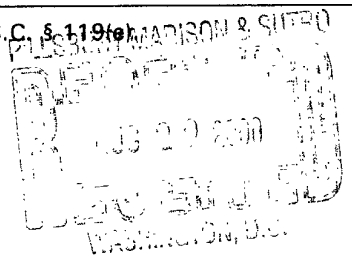
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).



Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Restriction and election

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 26-32, drawn to a method of marking sample with polymers, classified in class 427, subclass 7;

   II. Claims 33-38, drawn to a method of encoding and recovering information stored in a polymer, classified in class 536, subclass 25.3;

   III. Claims 39-76, drawn to a method of analyzing a target molecule, classified in class 435, subclass 6.

2. Inventions I, II and III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MEP. § 808.01). In the instant case the different inventions have different modes of operation in that the method of Invention I operates by addition of marker polymers to a sample; the method of Invention II operates by encoding information via polymer synthesis and in Invention III target molecules are analyzed by contacting with a collection of reagent-bearing substrates and an encoding system. Therefore, the functions and effects are also different in that in Invention I samples are marked thereby providing a means of identification; in Invention II a polymer is encoded with information thereby providing stored information and in Invention III the presence of a target molecule is detected.

3. Because these inventions are distinct for the reasons given above and the searches required for the three different inventions are not co-extensive restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Gary Tonegawa on June 12, 2000 a provisional election was made without traverse to prosecute Invention III, claims 39-76. Affirmation of this election must be made by applicant in replying to this Office action. Claims 36-38 are withdrawn from further consideration by the examiner, 37 CAR 1.142(b), as being drawn to a non-elected invention.

Substitute specification

5. The substitute specification filed July 28, 1999 will not be entered because it is incomplete. The document is replete with attorney docket numbers instead of application serial numbers throughout the specification. The substitute specification should be carefully reviewed prior to submission to ensure that all of the necessary amendments have been inserted.

Rejection under 35 U.S.C. 112, first paragraph: Lack of written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 39-76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention is a method of analyzing a target molecule in a sample by contacting the target with a collection of different substrates each bearing different reagents which bind to the target molecule wherein the method includes an "encoding system". The method of analyzing a target molecule via contacting with multiple reagents is described in the specification primarily with regard to making a positionally defined array of oligonucleotides or amino acids and as a hybridization reaction between a sample target nucleic acid and oligonucleotide probes in the array (pages 102-113). The "collection of substrates" is exemplified at pages 36-37 of the specification as a collection of beads which may be sorted after "contacting" according to the reagents which have bound to target molecules using sorting devices known in the art. The specification goes on to say that after sorting and collecting "the encoding scheme may be read off to determine the specificity of the reagent on the bead". The "encoding system" is next referred to in the specification in two sentences at page 37. It is stated therein that the "encoding system" may be "a magnetic system, a shape encoding system, a color encoding system, or a combination of any of these, or any other encoding system". While such systems were generally known in the art and colored beads for immobilizing

biological reagents, for example, were commercially available, the skilled practitioner in the art would not have known *a priori* which "encoding system" or combination of "encoding systems" would be workable with the claimed invention method absent some guidance in the specification. However, the specification fails to teach or provide guidance for selecting an appropriate "encoding system" or for combining two or more such systems or for making or using the claimed method of analysis with an "encoding system". There is no description of the chemical nature, i.e., the composition, of the encoding system or of the coding mechanism. Is not taught whether the "encoding system" is part of the substrate which bears the reagents or is a separate entity. In addition to enablement the first paragraph of 112 requires a "written description". As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. In the present case it is clear that applicant was not in possession at the time of filing of the claimed invention method with "encoding system" in view of the absence of teaching or guidance as to the nature of this "system" and how to make and use it with the claimed invention method.

Note: In view of the lack of written description as set forth above, the claims are entitled only to the filing date of the present application, July 28, 1999.

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 39-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The syntax is confusing in claims 39 and 58 and therefore in all of the claims because it is unclear whether the different substrates each bear an encoding system or the target molecule is contacted with a collection of substrates and with an encoding system. Clarification is required.

Rejections under 35 U.S.C. 102(b): Anticipation

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 39, 40, 42, 44, 47, 48, 52, 56, 58, 59, 61, 63, 66, 67, 71 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Mochida Pharmaceutical Co., Ltd. (Mochida herein). Mochida discloses the claimed invention method of claims 39, 40, 48, 52, 58, 59, 67 and 71 of analyzing a target molecule in a sample by contacting the target molecule with a collection of substrates having a three dimensional contour (beads) (page 2, lines 20-21) bearing different reagents (antibodies) and an encoding system (e.g., bar code) and identifying the reagents using the encoding system (bar code) (page 4, lines 18-50). Regarding claims 42, 44, 56, 61, 63 and 75, Mochida discloses that the target is a polymer: a peptide or polypeptide (page 4, lines 18-50). Regarding claims 47 and 66, Mochida discloses that the encoding system is a magnetic system (page 2, lines 28-28).

9. Claims 39-45, 48, 50, 52-64, 67, 69 and 71-76 are rejected under 35 U.S.C. 102(b) as being anticipated by the patent to Mandecki (5,641,634). Mandecki discloses the claimed invention method of claims 39, 48, 50, 52, 58, 67, 69 and 71 of analyzing a target molecule in a sample by contacting the target molecule with a collection of substrates having a three dimensional contour (glass beads (column 4, lines 16-23)) bearing different reagents and an encoding system and identifying the reagents using the encoding system (columns 10-11, claim 4). Regarding claims 40-45, 53-57, 59-64 and 72-76, Mochida discloses that the reagents and/or target molecules are polymers, oligomers, oligonucleotides, polynucleotides, polypeptides, peptides and nucleic acids (column 3, lines 46-62).

10. Claims 39-45, 47-50, 52-64, 66-69 and 71-76 are rejected under 35 U.S.C. 102(b) as being anticipated by the patent to Nova et al. (5,751,629). Nova et al. disclose the claimed invention method of claims 39-45, 47, 52-64, 66 and 71-76 of analyzing a target molecule in a sample by contacting the target molecule with a collection of substrates

having a three dimensional contour bearing different reagents and an encoding system and identifying the reagents using the encoding system (column 38, claim 1). Regarding claims 48-50 and 67-70 Nova et al. further disclose that the substrates are beads or fibers and comprise glass (column 16, lines 1-53).

Rejection under 35 U.S.C. 103(a): Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 46, 51, 65 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mochida Pharmaceutical Co., Ltd. (Mochida herein) as applied to claims 39, 40, 42, 44, 47, 48, 52, 56, 58, 59, 61, 63, 66, 67, 71 and 75 above (paragraph 8) and further in view of the patent to Southern (5,700,637). The claimed invention differs from the Mochida disclosure wherein the substrates are impregnated with a fluorescent molecule (claims 46 and 65) and wherein the substrates are glass microscope slides (claims 51 and 70). However, fluorescent-impregnated substrates for immobilizing biological molecules were known in the art and available from commercial suppliers. Microscope slides as substrates for immobilizing biological molecules were also known in the art as exemplified by Southern (column 8, line 59-column 9, line 36). It would have been **prima facie** obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Mochida with the teachings of Southern to obtain the claimed invention because the skilled practitioner in the art would have been motivated with a reasonable expectation of success by the obvious advantages of employing materials that were readily available.

Prior art of interest

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Durley, III et al. (5,075,077) disclose a method of analyzing a target molecule in a sample comprising contacting the target molecule with an array of different reagents and an encoding system in an apparatus for automated analysis.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. Zitomer
Stephanie Zitomer, Ph.D.
August 22, 2000

EXHIBIT 25

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

FODOR et al.

Appln. No. 09/362,089 Group Art Unit: 1655

Filed: July 28, 1999 Examiner: S. Zitomer

FOR: ANALYSIS OF TARGET MOLECULES USING AN ENCODING SYSTEM (as amended)

* * *

February 28, 2001

AMENDMENT UNDER 37 CFR § 1.111

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

Responsive to the Office Action mailed August 28, 2000 (Paper No. 9), entry and consideration of the following amendment and remarks are requested.

IN THE TITLE:

Kindly replace the title wherever it appears in the application (e.g., cover sheet, page 1, and page 142 of the substitute specification) with --ANALYSIS OF TARGET MOLECULES USING AN ENCODING SYSTEM--.

IN THE CLAIMS:

Kindly amend the claims as follows.

39. (Amended) A method of analyzing a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents [and an encoding system],

whereby one or more of the substrates bind to the target via the reagent, and an individual bound substrate thereby bears a tag of an encoding system;

(b) separating the substrates that bind the target from the substrates that do not bind the target; and

(c) identifying the reagent on a separated substrate [using the encoding system] by reading the tag on the separated substrate.

58. (Amended) A method of analyzing a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents [and an encoding system], whereby one or more of the substrates bind to the target via the reagent, and an individual bound substrate thereby bears a tag of an encoding system; and

(b) identifying the reagent on the substrate bound to the target [using the encoding system] by reading the tag on the individual bound substrate.

Kindly cancel claims 26-38 without prejudice and add the following claims:

--77. A method of analyzing a target nucleic acid in a sample, comprising:

(a) contacting the target with a collection of beads, wherein different beads bear different probe nucleic acids, whereby one or more of the beads bind to the target via hybridization between the probe and the target,

and an individual bound bead thereby bears a tag of an encoding system; and

(b) identifying the different probes on the one or more beads which are bound to the target by reading the tag on the individual bound bead.

78. A method of analyzing a target nucleic acid in a sample according to the method of claim 77 and further comprising sorting the one or more beads that bind to the target from beads that do not bind to the target.

79. The method of claim 78, wherein the beads are sorted with a cell sorting device.

80. The method of claim 77, wherein at least one of the different probes is an oligonucleotide.

81. The method of claim 77, wherein at least one of the different probes is a polynucleotide.

82. The method of claim 77, wherein the bead is tagged with a fluorescent tag of a color encoding system.

83. The method of claim 77, wherein the target nucleic acid has a label and hybridization results in the individual bound bead to be tagged with the label.

84. The method of claim 83, wherein the label is a green or red fluorescent label.

85. The method of claim 83, wherein the label is selected from the group consisting of radioisotopes, chemiluminescent or bioluminescent compounds, chromogens, heavy metal atoms, electron spin labels, magnetic labels, enzyme-linked labels, and labeled binding proteins.

86. The method of claim 77, wherein the encoding system is a magnetic system, shape encoding system, color encoding system, or a combination thereof.

87. The method of claim 77, wherein the collection of beads has at least 10^2 different probes.

88. The method of claim 77, wherein the collection of beads has at least 10^3 different probes.

89. The method of claim 77, wherein the collection of beads has at least 10^4 different probes.

90. The method of claim 77, wherein the collection of beads has at least 10^5 different probes.

91. The method of claim 77, wherein the collection of beads has at least 10^6 different probes.--

REMARKS

Reconsideration and allowance are respectfully requested.

Applicants acknowledge with appreciation the Examiner's courtesy in granting the interview of November 9, 2000.

Claims 39-91 are pending. Applicants affirm election of Group III (claims 39-76) in response to the Examiner's restriction requirement. Non-elected claims 26-38 were withdrawn from consideration by the Examiner. Applicants have canceled the non-elected claims without prejudice, and filed divisional applications directed to that subject matter.

It was indicated on page 3 of the Action that the substitute specification would not be entered because it is incomplete. In response, Applicants respectfully request that the Examiner review the original and substitute specifications, and ensure that they were not switched during processing of this application. If another copy of the substitute specification is required, Applicants would provide it to the Examiner.

The claim amendments are supported by the original disclosure and, thus, do not add new matter. If the Examiner should disagree, she is respectfully requested to point out the challenged limitation in the next Office Action so support can be cited in response. For example, claims 39 and 58 are supported by the disclosure from page 36, last paragraph, to page 37, second paragraph, of the substitute specification as applied to analysis of target molecules (e.g., sequence information, fingerprint information, or mapping information). New claims 77-91 were added to more

particularly describe the bead embodiment of the invention. Page 12, last paragraph, of the substitute specification describes different minimum numbers of probes on the substrates. Page 41, third paragraph; page 48, second paragraph; page 56, third paragraph; and pages 84-87 of the substitute specification show particular examples of tags and labels that can encode the bound substrate.

35 U.S.C. § 112 – Written Description

Claims 39-76 were rejected under Section 112, first paragraph, as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Applicants traverse because the guidance that the Examiner alleges would be required but is absent from this specification would have been known to persons skilled in the art at the time this application was filed. A patent need not teach, and preferably omits, what is well known in the art. *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

To clarify the use of the encoding system and its relationship to the substrate bound to target, the term "label" or "tag" has been used in the claims to indicate the entity that is to be read on the bound substrate and which identifies the reagent. Tag is used more generally as part of the encoding system, and label is used as a tag which is on the substrate through binding to the target (i.e., the target is labeled and the label is attached to the substrate through the target).

Applicants' substitute specification states on page 37, second paragraph, "An encoding system may include a magnetic system, a shape encoding system, a color

encoding system, or a combination of any of these, or any other encoding system." It was alleged on page 4 of the Action that a person skilled in the art "would not have known *a priori* which 'encoding system' or combination of 'encoding systems' would be workable with the claimed invention absent some guidance in the specification." But Applicants submit that this is an incorrect characterization of their disclosure and the general knowledge available to persons skilled in the art.

As quoted above, Applicants' specification teaches various encoding systems suitable for use in the claimed invention. The tags and labels suitable for use in an encoding system are described on page 41, third paragraph; page 48, second paragraph; page 56, third paragraph; and pages 84-87 of the substitute specification. A magnetic encoding system, for example, could use magnetic probes as taught on page 41, third paragraph, of the substitute specification or transponders as disclosed in the U.S. patents as cited by Mandecki on col. 5, lines 1 and 5, of U.S. Patent No. 5,641,634. Combining such systems would be routine given the skill in the art. Thus, such systems were known although they were not previously used as in the claimed invention. This shows that the chemical structure of the "encoding system" is taught in this specification and that person skilled in the art would know how to make and use such tags and labels as part of the encoding system.

When the description of the "encoding system" (pages 36-37) is read in light of the rest of Applicants' specification, especially the description of "coding" applications and the use of nucleotide sequences for encoding on pages 95-99 of the substitute specification, a person of skill in the art would recognize that the pending claims are supported by a broad disclosure of Applicants' invention.

It was further alleged on page 4 of the Action that it is not taught "whether 'the encoding system' is part of the substrate which bears the reagents or is a separate entity." Applicants submit that an explicit teaching in this specification is not required because the prophetic example on pages 36-37 of the substitute specification (i.e., reading the encoding system to determine the specificity of the reagent on the bead) implies that the tag of the encoding system is borne on the substrate at least after that substrate is bound to the target because sorting bound from unbound does not separate the tag from the bound substrate. Only if the bound substrate itself bears the tag could the encoding system be "read off" after sorting.

Another statement on page 4 appears to ask whether the encoding system and the substrate are "separate entities." This is answered by the implied teaching on page 37 of the substitute specification that it is the substrate bound to target which is encoded ("beads which do bind might be encoded"). Thus, depending on whether a tag of the encoding system is on the substrate or on the target before binding, the encoding system may or may not be attached directly to the substrate at the initiation of the process. For example, if the target was initially tagged then the substrate could become indirectly tagged after binding. But the tag may also be directly attached to the substrate and, thus, they would not be separate entities. In either situation, the encoding system would be borne by the substrate after binding to the target. Alternatively, Applicants describe intercalating dyes (e.g., ethidium bromide) that become part of the bound substrate by intercalating into the double helix of hybridized target and reagent on page 84, third paragraph, of the substitute specification. Such labels would be separate from the target, the substrate, and the reagent before binding and be read off the substrate after binding.

Applicants request withdrawal of the claim rejection made under Section 112, first paragraph, because this specification conveys to a person skilled in the art with reasonable clarity that Applicants were in possession of an encoding system that can be used in claimed invention. Their disclosure would also teach a skilled person, who possesses general knowledge available in the art, how to make and use tags of the encoding system suitable for the claimed invention.

Upon withdrawal of the rejection under Section 112, first paragraph, the latest priority date of this application would be December 20, 1990 because this application would be entitled to an earlier effective filing date under Section 120.

35 U.S.C. § 112 - Definiteness

Claims 39-76 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The syntax of claims 39 and 58 has been clarified in response to the objection raised on page 4 of the Action. In particular, the claims as amended make clear that (1) the reagent and tag are different entities, (2) an individual bound substrate bears a tag of an encoding system, and (3) the tag of the encoding system is on the bound substrate at least after binding.

Applicants request withdrawal of the claim rejection made under Section 112, second paragraph, because the pending claims are clear and definite.

35 U.S.C. § 102 - Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 39-40, 42, 44, 47-48, 52, 56, 58-59, 61, 63, 66-67, 71 and 75 were rejected under Section 102(b) as allegedly anticipated by Mochida et al. (UK Patent Appln. No. 2,129,551). Applicants traverse.

Mochida teaches a tag on an assay vessel or a reaction container. The tag can contain information about various characteristics of the assay. It also appears that the reagent may be on the assay vessel *per se* such that the vessel acts as a reaction container. When antibody reagents are on beads, however, the reference fails to disclose that the tag is on the bead. In such a situation, the assay vessel is tagged but the bound bead does not bear the tag.

Furthermore, even in those cases in which the substrate is tagged (i.e., the tag on the reaction container), Mochida does not separate the substrates that bind target via the reagent (i.e., bound substrates) from those that do not bind target (i.e., unbound substrates). Thus, claim 39 is not anticipated by the reference because the separation step is a required limitation of the method.

Assay information provided by the tag is apparently not directed to the identity of the reagent. Instead, Mochida discloses that the information given are characteristics such as the identity of the standard specimen, its lot number, and the calibration curve. Claims 39 and 58 are not anticipated by the reference because the reagent

cannot be identified by reading the tag on the bound or separated substrate. This failure is not surprising because identification of the reagent on the substrate is not Mochida's objective. Mochida apparently is only using one type of reagent for each assay instead of different substrates bearing different reagents. Thus, claims 39 and 58 are also not anticipated by the reference because providing different substrates bearing different reagents is a required limitation of both methods.

Mochida does not anticipate the claimed invention because all limitations of independent claim 39 or 58 are not found in the reference. Moreover, those claims depending from the independent claims are also not anticipated by the reference because the limitations of claims 39 or 58 are incorporated in the dependent claims. See *In re McCarn* 101 USPQ 411, 413 (C.C.P.A. 1954).

Claims 39-45, 48, 50, 52-64, 67, 69 and 71-76 were rejected under Section 102(b) as allegedly anticipated by Mandecki (US Patent No. 5,641,634). Applicants traverse because the reference is not prior art. The reference date of Mandecki is June 24, 1997 under Section 102(b) and November 30, 1995 under Section 102(e), but this application is entitled to a priority date of at least December 6, 1990 by a series of continuation and divisional application. Thus, Mandecki does not anticipate the claimed invention.

Claims 39-45, 47-50, 52-64, 66-69 and 71-76 were rejected under Section 102(b) as allegedly anticipated by Nova et al. (US Patent No. 5,751,629). Applicants traverse because the reference is not prior art. The earliest reference date that Nova et al. would appear to be entitled to under Section 102(e) is April 25, 1995, but this application is entitled to a priority date of at least December 6, 1990 by a series of

continuation and divisional application. Thus, Nova et al. does not anticipate the claimed invention.

For the above reasons, it is submitted that the claim rejections made under Section 102 should be withdrawn.

35 U.S.C. § 103 – Nonobviousness

To establish a case of *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references can be combined does not render the resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a *prima facie* case of obviousness without some evidence that supplies the impetus to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may

be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id*. Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 46, 51, 65 and 70 were rejected under Section 103(a) as allegedly unpatentable over Mochida et al. as applied to claims 39-40, 42, 44, 47-48, 52, 56, 58-59, 61, 63, 66-67, 71 and 75 above and further in view of Southern (US Patent No. 5,700,637). Applicants traverse.

The failure of Mochida to disclose the claimed invention is not remedied by the attempt to modify that disclosure with Southern. Among those failures are the lack of a separation step, the inability to identify the reagent by reading the tag on the bound or separated substrate, and the absence of different substrates bearing different reagents.

Apparently, Southern was cited for other reasons having to do with impregnating substrates with a fluorescent molecule and using glass microscope slides as substrates. But a review of Southern does not show that it addresses Mochida's deficiencies or even attempts to address those types of problems.

Finally, Applicants submit that there would be no motivation to combine the references or a reasonable expectation of success because of the disparate objectives and technologies of Mochida and Southern.

For the above reasons, it is submitted that the claim rejection made under Section 103(a) should be withdrawn because all limitations of independent claim 39 or 58 are not found or suggested in the cited references. Moreover, claims depending from those independent claims are also not made obvious by the references because the limitations of claims 39 or 58 are incorporated in the dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Having fully responded to the objections and rejections in the pending Office Action (Paper No. 9), Applicants submit that the pending claims are in condition for allowance and earnestly solicit an early Notice of same. If further information is needed, the Examiner is invited to contact the undersigned.

Respectfully submitted,

Intellectual Property Group of
PILLSBURY WINTHROP L.L.P.

By _____

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EXHIBIT 26

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/362,089	07/28/99	HOOR	PM-254814

HM22/0515

PILLSBURY MADISON & SUTRO LLP
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EXAMINER	
ZITOMER,S	
ART UNIT	**PAPER NUMBER**
1655	14

DATE MAILED: 05/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

RECEIVED
PILLSBURY WINTHROP LLP/DC
MAY 16 2001

CL# 71180 MT# 254814
ATTY(S) DNK GXT
DUE: AUGUST 15 2001
DKT BY (1) CMS (2) DMW

PTO-90C (Rev.11/00)
*U.S. GPO: 2000-475-249/45175

2 - Mail Copy

Office Action Summary

Application No.	Applicant(s)
09/362,089	FODOR et al.
Examiner	**Art Unit**
Stephanie Zitomer	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 28, 2001*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *39-91* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *39-91* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

CL# 71180 MT# 254814
ATTY(S) JNK KET
DUE: August 15 2001
DKT BY (1) JMS (2) OSW

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Application status

1. Receipt of the amendment filed February 28, 2001 is acknowledged.

2. The statement made in the previous Office action, paper no. 9 mailed August 28, 2000, regarding nonentry of the substitute specification is withdrawn in view of the discovery that due to a change in clerical procedure the substitute specification had been entered prior to the Office action.

3. The rejection in paper no. 9 at paragraph 6 of claims 39-76 for lack of proper written description under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to the claims and applicant's arguments. Withdrawal of this rejection restores the claims to the original priority date of December 6, 1990 and thus removes the prior art rejections set forth at paragraphs 8-11 which rejections are hereby also withdrawn. Applicant's arguments have been fully considered but are deemed moot in view of withdrawal of the rejections.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejection under 35 U.S.C. 112, first paragraph: Lack of written description

4. Claims 47, 66 and 86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention is a method of identifying a target molecule in a sample by contacting the target with a collection of different substrates each bearing different reagents which bind to the target molecule "and an individual bound substrate thereby bears a tag of an encoding system". The method of identifying a target molecule via contacting with multiple reagents is described in the specification primarily with regard to making a positionally defined array of oligonucleotides or amino acids and as a hybridization reaction between a sample target nucleic acid and oligonucleotide probes in the array (pages 102-113). The "collection of substrates" is exemplified at pages 36-37 of the specification as a collection of beads which

may be sorted after "contacting" according to the reagents which have bound to target molecules using sorting devices known in the art. The specification goes on to say that after sorting and collecting "the encoding scheme may be read off to determine the specificity of the reagent on the bead". The "encoding system" is next referred to in the specification in two sentences at page 37. It is stated therein that the "encoding system" may be "a magnetic system, a shape encoding system, a color encoding system, or a combination of any of these, or any other encoding system". While such systems were generally known in the art and colored beads for immobilizing biological reagents, for example, were commercially available, neither the specification nor any prior art cited therein describes how to make and use a magnetic encoding system to differentiate and identify individual bound substrates. In the amendment filed February 28, 2001 applicant cites page 41, paragraph 3, which mentions magnetic probes as an example of a "suitable label". Again, however, it is pointed out that the use of a magnetic encoding system for providing and reading the "tag of an encoding system" on "an individual bound substrate" as claimed is not described in the specification nor is any prior art cited therein that does describe such a system for use in the claimed invention method. The Court determined in *In re Glass*, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974) that the specification must be complete as of the filing date of the application, i.e., must contain such description and details to enable any person skilled in the art to make and use the claimed invention. In *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the Court determined that in addition to enablement the first paragraph of 112 requires a "written description" which must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the claimed invention. Clearly, in view of the foregoing, the specification fails to provide written description of the claimed method wherein a tag of a magnetic encoding system identifies an individual target-bound substrate.

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

5. Claims 39-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 39-57 are confusing in lacking proper antecedent basis for "tag of an encoding system" in (a) because binding a target to the substrate via a reagent does not "thereby" attach a "tag" to the substrate, the target or the reagent. Clarification is required.

(b) Claims 39-57 are confusing in lacking proper antecedent basis in (c) for "identifying the reagent" because "target molecule" implies that the target is the element to be identified in the method whereas no "identifying" function is recited for the "reagent". If the "reagent" is a "tag" it should be recited in the claim. Clarification is required.

(c) It is noted that the preamble to claims 39, 58 and 77, which in any case may not carry patentable weight, states that the method is for "analyzing" a target molecule whereas the outcome of the method is "identifying". It is noted further that the method is not a "method of analyzing" because "analyzing" is a method itself and thus requires method steps which are not recited in the claim.

(d) Claim 47 is confusing because "magnetic" and "shape" encoding systems are *non sequitur* to "tag" in claim 39. The relationships among "substrates", "reagents" and "tag" require clarification.

(e) In claim 52, "three dimensional contour" is noninformative in that all substrates have a "three dimensional contour". The claim also lacks proper antecedent basis in claim 39 because the "contour" has no function in the latter claim method. Furthermore, it is unclear whether "three dimensional contour" is intended to relate to the "shape encoding system" of claim 47. Clarification is required.

(f) Claims 58 and 77 and claims dependent therefrom are confusing in lacking proper antecedent basis for "tag of an encoding system" in (a) because binding a target to the substrate via a reagent does not "thereby" attach a "tag" to the substrate, the target or the reagent. Clarification is required.

(g) Claim 66 is confusing because "magnetic" and "shape" encoding systems are *non sequitur* to "tag" in claim 58 and claim 86 is confusing because "magnetic" and "shape" encoding systems are *non sequitur* to "tag" in claim 77. See above at (d).

(h) Claim 71 suffers the same inadequacies as claim 52. See above at (e).

Conclusion

6. **No claim is allowed.** However, the claims are free of the prior art.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S Zitomer

Stephanie Zitomer, Ph.D.

May 14, 2001

STEPHANIE ZITOMER
PRIMARY EXAMINER

EXHIBIT 27

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

FODOR ET AL

Serial No. 09/362,089 Group Art Unit: 1655

Filed: July 28, 1999 Examiner: Zitomer

For: ANALYSIS OF TARGET MOLECULES USING AN ENCODING SYSTEM

September 25, 2001
Via Facsimile

SUPPLEMENTAL AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Supplementing the applicants' amendment of September 17, 2001, please amend the above application as follows:

IN THE CLAIMS

Please enter the following amended claims:

39. (Thrice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different binding reagents and a binding reagent encoding system, whereby the target molecule binds to one or more of the substrates via the reagent;

(b) separating the substrates that bind the target molecule from the substrates that do not bind the target molecule; and

(c) identifying the reagent on a separated substrate by reading the binding reagent encoding system on the separated substrate and thereby identifying said bound target molecule.

47. (Twice Amended) The method of claim 39, wherein the encoding system is a magnetic system, shape encoding system, color endocing system, or a combination thereof.

58. (Thrice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molcule with a collection of substrates, wherein different substrates bear different binding reagents and a reagent encoding system, whereby one or more of the substrates bind to the target molecule via the binding reagent; and

(b) identifying the binding reagent on the substrate bound to the target by reading the reagent encoding system on the individual bound substrate and thereby identifying said target molecule.

66. (Twice Amended) The method of claim 58, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

77. (Twice Amended) A method of identifying a target nucleic acid in a sample, comprising:

(a) contacting the target nucleic acid with a collection of beads, wherein different beads bear different probe nucleic acids and a probe encoding system, whereby one or more of the beads bind to the target nucleic acid via hybridization between the probe nucleic acid and the target nucleic acid; and

(b) identifying the different probes on the one or more beads which are bound to the target nucleic acid by reading the encoding system on the individual target bound bead and thereby identifying said target nucleic acid.

78. (Twice Amended) A method of identifying a target nucleic acid in a sample according to the method of claim 77 and further comprising sorting the one or more beads that bind to the target nucleic acid from beads that do not bind to the target nucleic acid.

86. (Twice Amended) The method of claim 77, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

REMARKS

The applicants appreciate the courtesy and helpfulness extended by Examiner Zitomer to the undersigned at the interview on September 20th.

The claims have been amended as discussed with the Examiner in order to improve the form of the claims and the definition of the applicants' invention. The changes made in the claims are thought to be consistent with those discussed with the Examiner and allowance of the application is believed to be in order for the reasons advanced in the applicants' earlier response of September 17, 2001.

Claims 47, 66 and 86 have been returned to their previous form as it is understood that the Examiner agrees with the applicants that the various encoding systems recited in these claims find full support in the applicants' disclosure. See, for example, page 37, 1st full ¶ of the applicants' substitute specification.

The changes in the claims are highlighted in the attached Appendix.

Favorable action is requested.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By _____
Paul N. Kokulis
Reg. No. 16773

PNK:mh
1600 Tysons Boulevard
McLean, Virginia 22102
Phone: (703) 905-2118

APPENDIX

Version with Markings to Show Changes Made

IN THE CLAIMS

The claims have been amended as follows:

39. (Thrice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different binding reagents and [an] a binding reagent encoding system, whereby the target molecule binds to one or more of the substrates [bind to the target] via the reagent;

(b) separating the substrates that bind the target molecule from the substrates that do not bind the target molecule; and

(c) identifying the reagent on a separated substrate by reading the binding reagent encoding system on the separated substrate and thereby identifying said bound target molecule.

47. (Twice Amended) The method of claim 39, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

58. (Thrice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different binding reagents and [an] a reagent encoding system, whereby one or more of the substrates bind to the target molecule via the binding reagent; and

(b) identifying the binding reagent on the substrate bound to the target by reading the reagent encoding system on the individual bound substrate and thereby identifying said target molecule.

66. (Twice Amended) The method of claim 58, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

77. (Twice Amended) A method of identifying a target nucleic acid in a sample, comprising:

(a) contacting the target nucleic acid with a collection of beads, wherein different beads bear different probe nucleic acids and [an] a probe encoding system, whereby one or more of the beads bind to the target nucleic acid via hybridization between the probe nucleic acid and the target nucleic acid; and

(b) identifying the different probes on the one or more beads which are bound to the target nucleic acid by reading the encoding system on the individual target bound bead and thereby identifying said target nucleic acid [molecule].

78. (Twice Amended) A method of identifying a target nucleic acid in a sample according to the method of claim 77 and further comprising sorting the one or more beads that bind to the target nucleic acid from beads that do not bind to the target nucleic acid.

86. (Twice Amended) The method of claim 77, wherein the encoding system is a magnetic encoding system, shape encoding system, color encoding system, or a combination thereof.

EXHIBIT 28

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

FODOR ET AL

Serial No. 09/362,089 Group Art Unit: 1655

Filed: July 28, 1999 Examiner: Zitomer

For: ANALYSIS OF TARGET MOLECULES
USING AN ENCODING SYSTEM

September 17, 2001

AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action dated May 15, 2001, please amend the above application as follows:

IN THE CLAIMS

Cancel claims 52 and 71 without prejudice.

Please enter the following amended claims:

39. (Twice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system,

whereby one or more of the substrates bind to the target via the reagent;

(b) separating the substrates that bind the target from the substrates that do not bind the target; and

(c) identifying the reagent on a separated substrate by reading the encoding system on the separated substrate and thereby identifying said target molecule.

47. (Amended) The method of claim 39, wherein the encoding system is based on color.

58. (Twice Amended) A method of identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system, whereby one or more of the substrates bind to the target via the reagent; and

(b) identifying the reagent on the substrate bound to the target by reading the encoding system on the individual bound substrate and thereby identifying said target molecule.

66. (Amended) The method of claim 58, wherein the encoding system is based on color.

77. (Amended) A method of identifying a target nucleic acid in a sample, comprising:

(a) contacting the target with a collection of beads, wherein different beads bear different probe nucleic acids and an encoding system, whereby one or more of the beads bind to the target via hybridization between the probe and the target; and

(b) identifying the different probes on the one or more beads which are bound to the target by reading the encoding system on the individual bound bead and thereby identifying said target molecule.

78. (Amended) A method of identifying a target nucleic acid in a sample according to the method of claim 77 and further comprising sorting the one or more beads that bind to the target from beads that do not bind to the target.

86. The method of claim 77, wherein the encoding system is based on color.

REMARKS

Entry of this amendment for allowance or appeal is requested.

The applicants express their appreciation to Examiner Zitomer for helpfulness extended to applicants' representatives at interview on May 17th regarding this application at which time the various issues raised in the action were discussed.

While the applicants do not agree with the Examiner's position in rejecting claims 47, 66 and 86 under Section 112, 1st ¶, these claims have been amended in a way which is thought to obviate the Examiner's objections in anticipation of an allowance of the remaining claims. Applicants intend to present the appropriate arguments in later applications. The amendments are without prejudice to applicants' main claims, e.g. claim 39.

Claims 39, 47, 58, 66, 77, 78 and 86 have also been amended to avoid the Examiner's objections in the Section 112, 2nd ¶ rejection as set out in Section 5 of the action. The manner in which the amendments deal with each of the Examiner's objections 5(a)-(h) is thought to be self-evident. Claims 52 and 71 have been canceled without prejudice as redundant in view of the nature of the claims from which they depend.

With the present amendment, the application is thought to be in condition for allowance and such action is requested.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By _____
Paul N. Kokulis
Reg. No. 16773

PNK:mh
1600 Tysons Boulevard
McLean, Virginia 22102
Phone: (703) 905-2118

APPENDIX

Version with Markings to Show Changes Made

IN THE CLAIMS

Claims 52 and 71 are being canceled.

The claims have been amended as follows:

39. (Twice Amended) A method of [analyzing] identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system, whereby one or more of the substrates bind to the target via the reagent[, and an individual bound substrate thereby bears a tag of an encoding system];

(b) separating the substrates that bind the target from the substrates that do not bind the target; and

(c) identifying the reagent on a separated substrate by reading the [tag] encoding system on the separated substrate and thereby identifying said target molecule.

47. (Amended) The method of claim 39, wherein the encoding system is [a magnetic system, shape encoding system, color encoding system, or a combination thereof] based on color.

58. (Twice Amended) A method of [analyzing] identifying a target molecule in a sample, comprising:

(a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system, whereby one or more of the substrates bind to the target via the reagent; and

(b) identifying the reagent on the substrate bound to the target by reading the [tag] encoding system on the individual bound substrate and thereby identifying said target molecule.

66. (Amended) The method of claim 58, wherein the encoding system is [a magnetic system, shape encoding system, color encoding system, or a combination thereof] based on color.

77. (Amended) A method of [analyzing] identifying a target nucleic acid in a sample, comprising:

(a) contacting the target with a collection of beads, wherein different beads bear different probe nucleic acids and an encoding system, whereby one or more of the beads bind to the target via hybridization between the probe and the target[, and an individual bound bead thereby bears a tag of an encoding system]; and

(b) identifying the different probes on the one or more beads which are bound to the target by reading the [tag] encoding system on the individual bound bead and thereby identifying said target molecule.

78. (Amended) A method of [analyzing] identifying a target nucleic acid in a sample according to the method of claim 77 and further comprising sorting the one or more beads that bind to the target from beads that do not bind to the target.

86. The method of claim 77, wherein the encoding system is [a magnetic system, shape encoding system, color encoding system, or a combination thereof] based on color.

EXHIBIT 29

Redacted

EXHIBIT 30

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/907,196	07/17/01	BESEMER	

EXAMINER	
D	A1-32U63

ART UNIT	PAPER NUMBER
	6

HM22/1012

IVAN D. ZITKOVSKY, PH.D.
ATTORNEY AT LAW
6 FREEMAN CIRCLE
LEXINGTON MA 02421-7713

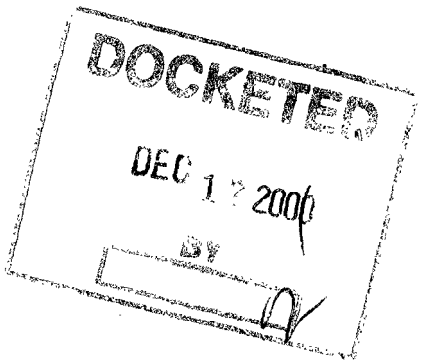
SIEW, J

DATE MAILED: 10/12/01

1656

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks



PTO-90C (Rev. 2/95)
*U.S. GPO: 2000-473-000/44602

2 - Mail Copy

Office Action Summary	Application No. 09/907,196	Applicant(s) BESEMER ET AL.
	Examiner Jeffrey Siew	Art Unit 1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2001* .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

SUPPLEMENTAL DETAILED ACTION

1. Due to cross mailing of preliminary of 10/1/01 , a supplemental office action is enclosed which supersedes the office action mailed 10/10/01.

Priority

2. If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Specification

3. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of t0he patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure

of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

As the instant application is drawn to agitation system for promoting the hybridization of target molecules to a nucleic acid array, a new abstract drawn to the claimed invention is required.

4. The Brief Description of the Drawings is objected to because the Drawings contain Figures 12a & 12b but the specification does not explicitly refer to them. Applicant is reminded that all Figures must be referenced in the Brief Description of Drawings.

Claim Objections

34

Claim 24 is grammatically awkward. The claim is drawn to probe array and further limited by the term probe array. The use of the word including after comprising is also awkward. The following is suggested "A probe array comprising different probes hybridized to targets and a bar code wherein the probes are deposited on a substrate arranged for scanning by a detection system".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsuhashi et al (US5,639612 June 17, 1997) in view of Clark et al (US5,358,691 Oct. 25, 1994).

Mitsuhashi et al teach a microtiter plate having a plurality of well having different polynucleotide probes immobilized for hybridization (see highlight sheet).

Mitsuhashi et al do not teach a bar code.

Clark et al teach an automated and continuous random access analytical system (see whole doc. esp. abstract). They teach the device has a bar code reader for reading off containers (see col. 19 lines 1-3).

One of ordinary skill would have been motivated to apply Clark et al's bar codes to Mitsuhashi et al's plates in order to provide random access information on the plate in a high throughput assay system. Bar codes were well known at the time the invention was made to provide for quick screening and identification. It would have been prima facie obvious to apply a bar code to Mistuhashi et al's plates in order to provide rapid identification of individual plates.

SUMMARY

7. No claim allowed.

CONCLUSION

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Siew whose telephone number is (703) 305-3886 and whose e-mail address is Jeffrey.Siew@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner is on flex-time schedule and can best be reached on weekdays from 6:30 a.m. to 3 p.m.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703)-308-1152.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist for Technology Center 1600 whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Center numbers for Group 1600 are Voice (703) 308-3290 and Fax (703) 308-4556 or (703) 308-4242.

Jeffrey Siew

October 8, 2001

EXHIBIT 31

Redacted

EXHIBIT 32

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